IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	Civil Action No. 05-356-SLR (consolidated)
		REDACTED PUBLIC VERSION

PLAINTIFFS' POST-TRIAL ANSWERING BRIEF

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INTRODUCTORY STATEMENT

The parties' experts in this case agree that Alzheimer's disease ("AD") is a tough and unforgiving disease that is "absolutely devastating" for the victims and caregivers alike. Levey 238:2; Raskind 1071:13 - 1074:17.[1] In January 1986, when Dr. Bonnie Davis applied for a patent on the use of galantamine to treat AD, **no drug** had succeeded in treating the disease. PX 1401; PX 1401A; Levey 289:20-290:4; Raskind 1120:9-16, 1080: 16-21. Today, more than 20 years later, only five drugs (including galantamine) have been approved by FDA for the treatment of AD, and of those, one (tacrine) is not prescribed because of safety concerns and another (Exelon) has tolerability problems that limit its use. Levey 286:3-287:23. The overwhelming majority of drugs tried as treatments for the disease — including the overwhelming majority of cholinesterase inhibitors (the class of compounds encompassing galantamine) — failed. PX 1401; PX 1401A; Levey 289:20-290:4; Raskind 1120: 9-16.

How did Dr. Davis succeed when so many others had failed? The answer is that she based her invention on a novel perspective that ran counter to the prevailing thinking in the art in 1986. As set forth in U.S. Patent No. 4,663,318 ("the '318 patent"), Dr. Davis recognized galantamine's then-unseen therapeutic potential in improving nicotinic cholinergic function in the brain, and perceived AD as a disease of the brain's nicotinic system. Coyle 888:12-889:12; Raskind 1189:20 - 1190:16.

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[1] This brief follows the same convention as Defendants' brief in citing trial testimony as "Witness page:lines." Dr. Murray Raskind is Vice Chairman of Psychiatry and Behavioral Sciences and Director of the Alzheimer's Disease Research Center at the University of Washington. He testified as an expert in the clinical testing and development of antidementia drugs (including drugs for AD). PX 1372. Dr. Joseph Coyle is Professor of Psychiatry and Neuroscience at Harvard Medical School and testified as an expert in neuropharmacology, behavioral pharmacology and pre-clinical testing of drugs for nerve degenerative disease. PX 1366. Drs. Levey and Domino were the Defendants' expert clinician and pharmacologist, respectively.

Dr. Davis' invention undeniably succeeds as a treatment for AD. Approved by FDA in 2001 as Reminyl® (now Razadyne®), galantamine meets the need, deeply felt in 1986, for treatment of the cognitive decline associated with AD. Levey 285:14-20. Razadyne IR has grossed over REDACTED in five years of sales. PX 1402; REDACTED . The experts agree that galantamine prevents deterioration of cognitive function, stabilizing the patient's condition, for roughly 12 months. Raskind 1167:15-19; Levey 109:7-14. The experts also agree that the drug improves the non-cognitive (behavioral) symptoms of the disease as well – a type of improvement Dr. Levey described in a 1999 article as "surprising and dramatic." Levey 238:24-239:2, 299:2-9. There is also substantial evidence that the drug slows progression of the disease. Coyle 927:7-928:3, 929:21-930:16; Raskind 1164:4-19, 1173:9-1174:1. It is thus beyond cavil that Dr. Davis succeeded where so many failed, inventing what has proven to be one of very few treatments now available for AD patients.[2]

To counter this clear record, Defendants attack the patent in two inconsistent ways, asserting either that the invention was anticipated and obvious or that it was merely an unscientific "guess." As will be shown below, Defendants' attack is at odds even with their own experts' testimony, which conceded both that the patent was scientifically grounded thereby enabling to a person of skill in the art to practice the invention (Levey 328:17-329:3, 330:23-331:1), and that the conventional wisdom at the time led away from a drug like galantamine that was seen as a weak and short-acting cholinesterase-inhibitor with predominantly peripheral and nicotinic effects (Levey 261:20-25, 276:16-20, 313:6-11). The trial record as a whole does not

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[2] In addition, seventeen drug companies sought the FDA's permission to make generic versions of the drug. The vast majority have acquiesced in the validity of the '318 patent and agreed to defer approval of their applications until the patent expires. PX 810, PX 811, PX 812, PX 818, PX 820, PX 1245, PX 1246, PX 1247, PX 1248, PX 1364, PX 1365.

come close to supporting Defendants' allegations of invalidity with the clear and convincing evidence that is required. To the contrary, the record establishes that Dr. Davis' invention was wholly novel and non-obvious and that, to use Dr. Coyle's phrase, adopted by Defendants (Def. Br. 45 (quoting Coyle 980:16-20)), her patent "connected the dots" so as to set forth a scientifically grounded basis for using galantamine as a treatment of AD and to enable a skilled artisan to practice the invention. The patent law requires no more.

Defendants' attack appears focused not on Dr. Davis's invention, but on the way she made it. According to Defendants, Dr. Davis' reliance on the technical literature instead of clinical trial data to support her invention is necessarily inadequate because, in their words, "[t]he patent either makes no innovative contribution to the art and is obvious, or it provides one of ordinary skill in the art with no evidence of utility and is not enabled." Def. Br. 3. But this is wrong both as a matter of law and fact, and Defendants' inability to say themselves whether the invention was patently obvious or overly speculative confirms that it is neither. Indeed, Defendants' attack is predicated upon a mischaracterization of Dr. Davis' invention. Dr. Davis did not merely reprint the prior art in her patent. Instead, she "connected the dots" in an entirely new and non-obvious way, combining unique insights into the therapeutic action of galantamine with a novel way of understanding the cholinergic deficiency in AD. This is the essence of a patentable invention: "Discovery consists of seeing what everyone has seen but thinking what nobody has thought."[3]

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[3] Albert Szent-Gyorgi (Nobel Laureate, Medicine). *See also In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998) ("As this court has often noted, invention itself is the process of combining prior art in a nonobvious manner.").

I. BACKGROUND TO ALZHEIMER'S DISEASE

A. Alzheimer's Disease

AD is a relentlessly progressive neurodegenerative disease of later life. It begins with "insidious onset of [] memory problems, which progress over time to develop into more serious memory problems, and then begins to affect other higher brain functions, such as judgment and reasoning, such as language ability, such as perception and recognition." Levey 100:2-19. As the disease progresses, sufferers may exhibit a range of neuropsychiatric symptoms, including depression, agitation and irritability, uncooperativeness, sleep disturbances, and paranoia. Raskind 1071:13-1072:20; Levey 100:2-19. The burden on family members and other caregivers can become overwhelming, and the rise in behavioral disturbances such as incontinence often simply exhausts the caregiver, leading to institutional placement. Raskind 1071:13-1072:20; Kauffman 1015:4-16. The disease is "absolutely devastating." Levey 238:2.

The hallmark pathologic feature of AD is plaques and neurofibrillary tangles in the brain. Def. Br. 4; Levey 318:3-4. Plaques and tangles are believed to disrupt neurotransmission, thereby interfering with cognition; ultimately, the affected neurons die. PX 663 at 1187. By 1986, three dementias were known to be characterized by plaques and tangles: Alzheimer's Disease, Senile Dementia of the Alzheimer's Type, and dementia in Down's Syndrome. PX 663 at 1184, 1188; Coyle 855:22-860:11; Levey 317:22-318:24. For convenience, all three will be referred to collectively as AD.

B. The Lack Of A Treatment In 1986

In 1986, when Dr. Davis applied for her patent, there were no treatments for AD, and hence doctors had no way even to alleviate the cognitive decline at the heart of the disease. Raskind 1080:16-21; Levey 283:25-285:6. In a 1985 publication, Dr. David Drachman – one of the fathers of the cholinergic deficit hypothesis and a leader in the AD field (Raskind 1087:16-

24) – observed that "[d]espite sporadic reports of barely detectable improvements with various drugs or drug combinations, therapeutic efforts have, in general, failed to produce improvement of clinical value." PX 213 at 307. In 1989 (three years after Dr. Davis applied for her patent), in introducing FDA's Anti-dementia Drug Assessment Symposium intended to promote the development of treatments for AD (Raskind 1081:8-1083:10), Dr. Paul Leber, director of the division responsible for AD treatments, observed that, "[a]t this point in time, even a safe and effective symptomatic treatment for some cardinal sign and symptom of Alzheimer's would constitute a substantive therapeutic advance." PX 1122 at 10; Raskind 1083:15-1084:4. At the symposium, Dr. Drachman was more direct: "we don't have any drugs that are really doing a hell of a lot." PX 1122 at 38; Raskind 1088:1-11.

The lack of a treatment was not for want of interest or effort. Defendants admit that by 1986, AD was recognized as the leading cause of dementia. Def. Br. 4. The disease was known to be epidemic among the nation's elderly, with some 2.5 million Americans estimated suffering from the disease. PX 1321 at 2; Raskind 1077:14-1078:9. The economic toll was estimated in the tens of billions of dollars. PX 1321 at 2-3. And the AD landscape was littered with failed attempts at treatment. PX 714; PX 1401.

C. The Cholinergic Deficit Hypothesis

In 1986, there was not even a general consensus that addressing the cholinergic deficit was the right course for developing an AD treatment. To the contrary, the cholinergic deficit hypothesis was one of many competing hypotheses – such as improving blood flow, increasing brain metabolism, and enhancing neuronal protection – pursued at the time. Raskind 1120:9-1122:10; PX 631; PX 714; PX 1401. While Defendants assert that only the cholinergic deficit hypothesis was supported by what they call "proof of concept," in fact the vast number of failed approaches makes plain that, to one of ordinary skill, each had its supporting rationale and it was

simply impossible to predict which approach, if any, might succeed. Raskind 1122:5-10.

By 1986, it was recognized that AD was associated with, among other things, the death of cholinergic neurons in the brain. PX 663. The cholinergic deficit hypothesis grew out of the observed loss of cholinergic neurons in the brains of AD sufferers autopsied after death and the observation that administration of scopolamine, a selective blocker of the muscarinic cholinergic receptors, mimicked the memory loss of old age. PX 663 at 1184; PX 632 at 338; Coyle 861:9-862:18. This led some researchers to seek to develop a treatment for AD through pharmacologic efforts intended to enhance cholinergic function. Levey 127:25-128:3. This effort, however, took many forms, including not just cholinesterase inhibitors (an intra-synaptic approach), but also acetylcholine precursors (a pre-synaptic approach) and muscarinic agonists (a post-synaptic approach). Levey 128:13-129:18; Raskind 1127:1-10.

Importantly, the cholinergic deficit hypothesis was narrowly focused on just a part of the cholinergic system – the muscarinic receptors in the brain. Cholinergic receptors are found throughout the body and brain. Levey 260:8-10; 16-18. In addition, there are two distinct families of cholinergic receptors, nicotinic receptors and muscarinic receptors. PX 1399; Domino 491:23-24 ("They are totally different receptors…. They have a totally different type.").

In the body, nicotinic receptors are found in the neuromuscular system, and neuromuscular disorders such as myasthenia gravis and curare poisoning were known to be associated with a loss of peripheral nicotinic cholinergic function. Levey 262:1-263:24; Coyle 882:23 - 883:6. Muscarinic receptors are found in the gut, and peripheral muscarinic cholinergic effects include the so-called "SLUD" syndrome: salivation, lacrimation, urination, and diarrhea. Domino 463:12-18; Davis 714:8-12.

Muscarinic and nicotinic receptors are also found in the brain. Central muscarinic

function was associated with memory. The role of central nicotinic receptors, by contrast, was not well understood. Levey 316:9- 317:6. To Dr. Davis, those receptors were associated with attention – in her view, a fundamental component of learning. Davis 694:13-15; 697:21-698:9.

The experts in this case agree that, in 1986, the cholinergic deficit hypothesis was focused on the muscarinic cholinergic system in the brain. This was in part due to the muscarinic system's known association with memory and studies showing that the muscarinic receptor blocker scopolamine induced a loss of memory similar to geriatric memory loss. This focus on central muscarinic receptors was further confirmed by the failure of nicotinic receptor blockers to have a similar effect on memory. PX 632 at 338; Levey 273:4-16. In Dr. Levey's words, "Really the field, the state of the art in 1986, was the vast majority of people thought that muscarinic receptors, the preponderance of evidence was that muscarinic receptors was the class that was most important for the symptomology of Alzheimer's disease." Levey 259:7-11.

Thus, researchers following a cholinergic approach looked for drugs having a strong central muscarinic effect. Dr. Raymond Bartus, in his influential 1982 *Science* article on the cholinergic deficit hypothesis, instructed that "the more directly one stimulates the muscarinic receptor, the more robust and consistent are the effects on memory performance in aged subjects." PX 653 at 414; Levey 265:9-20, 267:18-268:10. Levey and his co-authors similarly observed in 1995 that, from about 1985, they had "specifically focused on the muscarinic acetylcholine receptors since they are the primary targets of any cholinergic replacement therapies." PX 1223; Levey 303:6-17. This approach led away from drugs that had weak muscarinic effects and might instead enhance nicotinic function. Levey 268:8-10; 273:17-21.

D. The Understanding Of Galantamine In 1986

In 1986, galantamine was thought to be a weak cholinesterase inhibitor, with a potency less than a tenth that of physostigmine. Domino 416:3-9; Coyle 908:23-909:13. It was also

thought to be short-acting, with a duration of action similar to physostigmine (which was thought to be too short-acting to serve as a treatment for AD). Levey 334:15-23, 335:4-20; Raskind 1147: 3-10; Domino 391:2-10, PX 756 at 301. As Dr. Coyle explained, low potency would be undesirable because "that means you have to use more of it .... and the more of it you have to use, the greater the likelihood that the drug is going to interact with some other processes and cause side effects." Coyle 909:2-7.

Two other aspects of galantamine are worth mentioning. First, as Dr. Levey admits, the prior art described galantamine as having principally peripheral and nicotinic effects. Levey 264:3-5; *see also* PX 1181 at 5984; Coyle 911:15-20. The cholinergic deficit of AD, by contrast, is central and was thought at the time to be muscarinic, so a peripheral nicotinic agent would not be an attractive candidate. Raskind 1142:7-22; Coyle 915:7-10; Levey 261:20-25. Second, galantamine was understood to have weak muscarinic effects. Levey 312:25-313:11 (discussing Cozanitis, PX 1339), 316:19-23 (discussing Stojanov, PX 1350). Dr. Levey admitted that, to a person of ordinary skill, a weak muscarinic agent would not have appeared worth trying as a treatment for AD. Levey 268:8-10, 273:13-21, 276:16-20.

In sum, the properties of galantamine known in 1986 – a short-acting, weak cholinesterase inhibitor whose effects appeared predominantly peripheral and nicotinic – combined with the central muscarinic focus of the cholinergic deficit hypothesis at the time and the prevailing concern with peripheral cholinergic side effects, would have made galantamine appear a particularly **unpromising** cholinesterase inhibitor. Coyle 908:15-915:10.

II. DR. DAVIS' INVENTION AND THE '318 PATENT

A. Dr. Davis' Invention

Dr. Davis is a medical doctor whose research focus has been in neuroendocrinology, the study of the relationship between brain function and hormonal release in the body. B. Davis

686:4-690:2. In addition, beginning in the 1970s, Dr. Davis gained early experience with the behavior of the cholinergic system, and its relationship to memory function and memory disorders, through her work with her husband, Dr. Ken Davis, who has since established himself as a leading researcher in AD (and is now the President of the Mount Sinai Medical Center in New York). B. Davis 690:3-691:15; K. Davis 1031:18-23.

Through her work, Dr. Davis developed a "neuroendocrine window" that allowed her to understand the effects that cholinergic drugs had on the brain by measuring hormone levels in the blood. B. Davis 698:19-711:21; PX 1400. Using this "neuroendocrine window," Dr. Davis was able to deduce the effect a drug had on the central cholinergic system by looking at changes in certain hormones (principally cortisol and ACTH) and, indeed, to distinguish between central nicotinic and muscarinic effects. She found that changes in basal cortisol levels could be correlated with a drug's effects on central nicotinic function. B. Davis 700:16-701:9. By contrast, diurnal cortisol levels (that is, changes in overnight cortisol levels) showed a drug's effect on central muscarinic function. B. Davis 701:11-24. In short, rather than guess at a drug's effect on the central cholinergic system from its mechanism of action (such as its potency as a cholinesterase inhibitor), Dr. Davis was able to infer its actual effect from measurements of blood hormone levels. K. Davis 1056:16-24.

At the same time, Dr. Davis' experience studying the cholinergic system and memory disorders led her to reject the conventional wisdom concerning the muscarinic nature of the cholinergic deficit in Alzheimer's. To Dr. Davis, AD was not just a disease of memory but also of learning. B. Davis 696:18-697:15. And, to her, learning was not just a matter of memory, but also of attention – a central nicotinic effect. B. Davis 697:21-698:9. This led her to look beyond muscarinic function for a cholinergic agent that would enhance nicotinic function as well.

In Dr. Davis' words, the prevailing muscarinic focus "was missing half the story." B. Davis 713:10-25. Instead, Dr. Davis adopted an "animal lesion" model for AD that involved destroying a portion of the brain (the nucleus basalis of Meynert) responsible for producing acetylcholine. PX 1 at col. 2, ll. 45-56; B. Davis 831:1-20. To Dr. Davis, this model was significantly superior because it gave "the same diminution of acetylcholine that one would get in early to moderate Alzheimer's," thereby yielding a chronic reduction in both muscarinic and nicotinic function. B. Davis 831:14-832:10; *see also* Coyle 886:21-888:8.

Armed with her insights concerning the neuroendocrine window and the need for enhancement of the central nicotinic system, Dr. Davis was able to bring a new perspective to bear on the existing technical literature. And out of the large body of literature she reviewed, she focused upon the work of Dr. Demitri Cozanitis, a leading researcher on galantamine. B. Davis 739:4-740:10. Dr. Cozanitis reported on studies showing a sustained (greater than 6 hour) rise in cortisol following the administration of galantamine along with the muscarinic blocker atropine. PX 829; B. Davis 706:20-707:1.

To Dr. Cozanitis and his colleagues, this rise appeared to indicate a generalized stress response. B. Davis 707:2-708:8. But to Dr. Davis, it was clear that the rise in cortisol from galantamine was not due to a stress response but instead was "a specific central stimulation of the nicotinic pathway." B. Davis 709:1-710:9. It was this recognition, from the results published by Cozanitis, of galantamine's sustained effects on the central nicotinic system, when combined with her insight on the importance of the nicotinic effects in addressing the cholinergic deficit of AD, that first led her to conceive her invention of using galantamine as a treatment for that disease. B. Davis 739:14-740:10.

Dr. Davis' focus on galantamine's sustained nicotinic effect allowed her to overcome

many of the other stumbling blocks that had confronted AD researchers. Because she recognized galantamine as a strong nicotinic agent but a weak muscarinic one, she was able to avoid the problem of peripheral cholinergic side effects, which were principally muscarinic in nature. B. Davis 714:3-19.[4] Similarly, Dr. Davis was not deterred by galantamine's lack of potency, since she knew from her analysis of Cozanitis' published data that, regardless of potency, galantamine actually worked to enhance central nicotinic function. B. Davis 715:2-10. Thus, because she could infer the actual effects of galantamine on central cholinergic function from published data, she was undeterred by the otherwise discouraging implications of galantamine's weak mechanism of action.

Having conceived of using galantamine for AD, Dr. Davis then sought to procure (unsuccessfully) a sample of galantamine for preclinical studies. B. Davis 715:13 - 718:15; PX 121; PX 122; PX 123. Between the conception of her invention and the filing of her patent application, she spent years further studying the literature on AD and on galantamine, and working as part of a research team testing other cholinergic drugs, notably physostigmine, on AD patients. B. Davis 740:22 - 741:12. This experience confirmed for her that galantamine was a viable treatment for AD and that the field's focus on muscarinic enhancement was misguided. B. Davis 741:13-743:4.

B. The '318 Patent

In the mid-1980s, upon becoming aware of method of treatment patents, Dr. Davis decided to pursue a patent for her invention in order to promote the development of galantamine for AD. K. Davis 1051:15-1052:1. Her patent application eventually issued as the '318 patent

[4] To a person of ordinary skill, galantamine's weak muscarinic effects risked exacerbated side effects, since the need to greatly increase the dose in order to achieve muscarinic enhancement would result in such side effects. Levey 276:16-20; Coyle 1006:11-1007:12.

that is at issue in this case.

The patent describes Dr. Davis' invention in the manner in which she had conceived it: that is, it sets forth both the evidence concerning galantamine's effects that she had perceived from a neuroendocrine approach and the new, broader model for AD. The '318 patent begins by describing the effects of galantamine administration on the central cholinergic system, starting with Cozanitis' work demonstrating a rise in the cortisol levels from the administration of galantamine with the muscarinic-blocker atropine. PX 1 at col. 1, ll. 11-21. In the context of the patent, this indicates that galantamine was enhancing central nicotinic function. Raskind 1181:13-1182:7; *see also* B. Davis 829:9-830:21. It then discloses additional properties of galantamine, including its effect on the central nervous system and its potential to improve short-term memory in animals. PX 1 at col. 1, ll. 22-25; PX 1 at col. 1, ll. 26-38; Raskind 1183:9-24.

The patent sets forth the selective lesion model of AD. PX 1 at col. 2, ll. 45-57. As noted, this model departs from the muscarinic-receptor focus then prevailing for the cholinergic deficit of AD because the new model incorporates sustained nicotinic effects. Coyle 888:2-8. A person of ordinary skill would recognize these differences. Raskind 1186:12-1187:12. This point would be reinforced by the patent's description of cognitive deficits induced by the selective lesion as "including the inability to learn and retain new information", that is, as a loss of learning and not just memory – effects that also would be recognized as nicotinic as well as muscarinic. Raskind 1187:13-20. In short, the patent combines data concerning galantamine's actual effects on the central cholinergic system with a description of the cholinergic deficit of AD that renders galantamine's effects therapeutically relevant.[5]

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[5] The patent also tells skilled artisans how to implement the invention. The patent describes the process of titration that one of skill in the art would use to arrive at an effective dose of (continued...)

After filing her patent application, in mid-1986, Dr. Davis finally obtained a sample of galantamine, and she approached Dr. Joseph Coyle, then of Johns Hopkins, with her invention of using galantamine to treat AD. She described her insight concerning galantamine's central nicotinic effect and asked Dr. Coyle whether he would be willing to test the drug. Coyle 888:12-889:12. As Dr. Coyle testified, Dr. Davis' proposal was "well grounded" and "fit in nicely with the lesion model where you could really see if there was a contribution of nicotinic receptors." Coyle 890:3-9. As he further explained, "[S]he had a proposal that connected the dots…in a model in which there is degeneration of cholinergic neurons in both nicotinic and muscarinic receptors…Galantamine in humans safe and well tolerated. Cholinesterase inhibitor, selective nicotinic effects, and very modest muscarinic receptor side effects." Coyle 980:16-981:1

During the prosecution of the '318 patent, the patent examiner issued an office action rejecting the pending claims in light of prior art indicating that galantamine had been shown to be beneficial in improving short term memory loss in dogs and reversing the effects of scopolamine-induced amnesia. PX 2 at 25-27. In response, Dr. Davis distinguished AD from other forms of memory loss on the basis of the unique pathology of AD. PX 14 at 4 ("It is true that in Alzheimer's disease, there is memory loss. However, this is apparently associated with physiological changes in the brain including the degeneration of nerve cells in the frontal and temporal lobes, damage in the neural pathways to the hippocampus and the creation of neurofibrillary tangles in nerve cells.") She also noted the problems with safety and tolerability in treating AD, pointing to physostigmine's "poor therapeutic index" and "problems of possible

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galantamine for the treatment of AD. PX 1 at col. 1, ll. 64-66. The patent establishes preferred doses for galantamine hydrobromide that coincide with the actual approved doses for galantamine. *Compare* PX 1 at col. 2, ll. 60-66 *with* DX 655.

toxicity." PX 14 at 2.

Dr. Davis made the patent examiner aware of the on-going testing of galantamine with the animal lesion model to confirm galantamine's utility and stated that she would submit results from those ongoing studies as they became available in the following "two or three months." PX 14 at 2. However, the patent examiner allowed the claims less than six weeks later, without waiting for further data. Notice of Allowability (in PX 2).

The patent issued on May 5, 1987, with seven claims. The claims at issue in this case are claims one and four. Claim 1 claims a method of treating AD and its related dementias by administering a therapeutically effective amount of galantamine or its salts. PX 1 at col. 3, ll. 6-10. Claim 4 is a dependent claim of claim 1 which claims an oral administration of galantamine or its salts within a dosage range of 10-2000 mg a day. PX 1 at col. 4, ll. 3-5.

III. DEVELOPMENT OF A GALANTAMINE DRUG PRODUCT

After receiving her '318 patent, Dr. Davis sought to develop her invention into a human drug product by attempting to interest a pharmaceutical company in taking galantamine through clinical trials. B. Davis 727:19-728:22. Dr. Davis contacted more than 30 pharmaceutical companies and was rejected by all but three – Ciba-Geigy, Shire[6], and Janssen. PX 1398; PX 1397.

The record reflects the research community's skepticism of galantamine's prospects. For example, in September 1987, The Upjohn Company rejected galantamine because Upjohn was "already committed to other mechanistic approaches to Alzheimer's disease which [it] consider[ed] more promising than that offered by galantamine." PX 586. Wyeth

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[6] Shire licensed foreign counterparts of the '318 patent. PX 1397.

Pharmaceuticals twice rejected galantamine. In 1987, the company did so because it concluded that "the potential for success of tacrine and physostigmine and other anti-cholinesterase products is not very positive." PX 596; Abou-Gharbia 1427:22-1428:3. The next year, after Dr. Davis provided additional data in support of her proposal, Wyeth again turned her down, explaining that "[t]here is still skepticism regarding the success of cholinesterase inhibitors in the treatment of senile dementia." PX 323; Abou-Gharbia 1430:8-16.

In 1989, Bristol-Myers Squibb rejected galantamine, stating that: "Unfortunately, clinical experience with galantamine in Alzheimer's patients is, presently, very limited. Therefore, the therapeutic benefit and long-term safety and tolerability of galantamine is still a matter of speculation." PX 119.

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Finally, in September 1990, Dr. Davis successfully licensed the '318 invention to Ciba-Geigy ("Ciba"). PX 305. Pursuant to the license, Ciba performed animal toxicology studies and a clinical study. B. Davis 758:19-24. The results from the toxicology study were positive, and the clinical study indicated the galantamine would have efficacy for the treatment of AD. B. Davis 758:25-759:9. In November 1993, Ciba terminated its license agreement, "without having any doubts with either the efficacy or the safety of galantamine." PX 833 at SYNRAZ 0015429; PX 467. After Ciba terminated its license, Dr. Davis "had to start all over again" to find a company to develop galantamine for the treatment of AD. B. Davis 763:17-764:3. In November

[7] Ironically, Defendant Mylan Pharmaceuticals (which filed an ANDA in 2005 for a generic galantamine drug product) rejected galantamine in April 1990, stating that the development of a galantamine product was inconsistent with its current research program. PX 173.

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1995, Dr. Davis licensed her invention to Janssen. PX 329. Janssen completed the pivotal clinical studies, which were positive, and on February 28, 2001, FDA approved galantamine for the treatment of mild to moderate AD. B. Davis 768:25-769:12.

ARGUMENT

I. CLAIM CONSTRUCTION

The parties are in agreement that just two terms of the '318 patent need construction: "Alzheimer's disease and related dementias" and "method of treating" (in the context of providing a therapeutically effective amount to AD patients). Def. Br. 15. Of course, claim terms are to be given their ordinary and customary meaning as would be understood by a person of ordinary skill reading the patent and prosecution history. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*). The parties are also in agreement that the meaning ascribed to the terms by a person of skill may be illuminated by the trial record. Pretrial Conf. Tr. at 7:1-15; *see also C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004).

1. "Alzheimer's disease and related dementias"

The parties agree that the term "Alzheimer's disease" refers to presenile dementia of the Alzheimer's type, in accord with the traditional meaning of the term and with the definition in the patent. PX 1, col. 1, l. 34; Def. Br. 4 n. 2. The parties also agree that the "classic pathological hallmarks" of AD are plaques and tangles. Def. Br. 4; Coyle 858:11-13; Levey 318:3-4. Indeed, in the prosecution history, Dr. Davis distinguished AD from other forms of memory loss, such as Wernicke-Korsakoff syndrome, on the basis that AD is characterized by plaques and tangles and "[t]here is no way of predicting that because a chemical may have an effect on memory in a normal brain (which is what is indicated in the cited references) it would have any effect on a brain that has suffered such physiological changes." PX 14 at 4. The term "Alzheimer's disease

and related dementias" would thus be understood by a person of ordinary skill reading the patent to include those dementias characterized by AD's "physiological changes" – that is, by the pathology of plaques and tangles. That encompasses three dementias: Alzheimer's Disease, Senile Dementia of the Alzheimer's Type, and dementia in Down's Syndrome. PX 663 at 1184, 1188; Coyle 857:25-858:13, 860:9-11; Levey 317:22-318:24.

2. "method of treating"

The ordinary meaning of the term "treating" in the context of AD is to alleviate the cognitive decline associated with the disease in a therapeutic way – that is, in a safe, effective, and clinically meaningful way. Defendants dispute that issues of safety, tolerability, and clinical utility apply to a method of treating AD and contend, rather tautologically, that a method of treating "simply means that the drug has to work." Def. Br. 16. But Defendants' own experts conceded that persons of skill in the art recognized at the time that one of the key challenges to developing a treatment for AD was finding a drug that would be not only effective, but safe and tolerable as well. Domino 465:4-14; *see also* Levey 352:22-23 ("everybody realized what you really needed is to overcome the safety issues, the side effect issues"). The prosecution history reflects these concerns, noting the "poor therapeutic index" and "problems of possible toxicity" associated with physostigmine. PX 14 at 2. Hence, a person of ordinary skill at the time would have recognized that, for a drug to "work" as a treatment for AD (to use Defendants' phrase), the drug would have to be safe and tolerable, as well as effective.

A similar analysis applies to the need for clinically meaningful results. As Dr. Raskind explained at trial, it was generally recognized in the art that it was not enough simply to help the patient do better on standard memory tests – to be a treatment for AD, the drug's effects must translate to the patient's overall daily function:

> if one shows a modest improvement on some cognitive reading or performance scale, but there is no evidence that the drug is also improving overall function, either in activities of daily living or the observational judgment of the caregiver or other person living with the patient, that, yes, indeed, they are doing better in their day-to-day activities and life, then you don't have a drug which can be considered effective. (Raskind 1093:6-14)

Though this statement derives from FDA's 1989 symposium, this understanding of what it means to treat dementia was widely shared in the field in 1986. Raskind 1092:21-1093:2. Indeed, the prior art adduced by Plaintiffs is replete with concerns about the clinical significance of the results. *E.g.* PX 763 at 1423 ("An inevitable question in any study of cholinomimetic agents in Alzheimer's disease is the clinical significance of the drug's effect."). Thus, here too, a person of ordinary skill at the time would have recognized that, for a drug to "work" as a treatment for AD (to again use Defendants' phrase), the drug must provide a clinically meaningful benefit, in addition to being safe and tolerable.

II. BHASKER DOES NOT ANTICIPATE THE '318 PATENT

Defendants contend that P.A. Bhasker's "Medical Management of Dementia," The Antiseptic: 70(1):45-47 (1974) (DX 483), anticipates the '318 patent because, according to Defendants, the article "discloses the use of galanthamine as a treatment for irreversible progressive dementias like AD" Def. Br. at 19. But Defendants' argument is flatly contradicted by the text of the Bhasker article and is wholly unsupported by the record evidence.

Central to Defendants argument is their contention that Bhasker describes the use of galantamine in connection with progressive dementias like AD. But Bhasker mentions galantamine only once, and does so only in connection with the entirely different context of local brain damage:

> The restoration of higher cortical function is difficult and was once considered to [be] impossible; but it has lately gained importance. Luria and his colleagues have dealt with this problem in great

> detail. They have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct, etc., by deinhibitory procedures and re-education of the rest of the brain. Deinhibition refers to the facilitation of acetylcholine activity by giving small daily doses of Cholinesterase inhibitors (Neostigmine, Gallanthamine etc.).

DX 483 at 46. Defendants' experts conceded that "local brain damage like tumour, head injury, infarct, etc." are **not** AD, but are instead forms of "arrested dementia" entirely distinct from progressive dementias like AD. Levey 218:2-21; Domino 488:10-13.

Indeed, Bhasker begins by classifying dementias into three distinct types – reversible, arrested, and irreversible – and stresses "the importance of thorough diagnosis" in making treatment decisions. DX 483 at 45. Thus, Bhasker itself expressly emphasizes the distinction in treatment between arrested dementias such as "local brain damage like tumour, head injury, infarct, etc." (Levey 209:14-25) and progressive dementias, which Defendants contend encompass AD (Levey 210:15-24). Bhasker's reference to galantamine is thus limited to the context of arrested dementias and has nothing to do with AD. As Dr. Levey elaborated:

> Q. … Now, Doctor, was [Bhasker] an article about local brain damage?
>
> A. It was an article about dementia as the title clearly alluded to and local brain damage as he would clearly give – can cause a form of dementia, which he considered arrested dementia.
>
> Q. And so what do you take this reference to daily doses of cholinesterase inhibitors like galanthamine to mean?
>
> A. To me, it's absolutely inherent in this paper where he's putting this in context that he's suggesting cholinesterase inhibitors might be tried for treating dementia, arrested dementia. That one might restore cortical functions, as has been shown to be the case for local brain injury. (Levey 219:14-220:3)

Two other aspects of Bhasker confirm that it does not describe galantamine as a treatment for AD. First, Bhasker expressly states that progressive dementias are untreatable. Specifically,

it states: "With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." DX 483 at 45. Thus, far from suggesting galantamine as a treatment for AD, Bhasker instead expressly states that no treatment is possible.

Second, Bhasker does not distinguish, in its reference to cholinesterase inhibitors, between galantamine and neostigmine. Levey 324:1-4; Coyle 938:7-939:6. Neostigmine is a peripheral cholinesterase inhibitor that does not readily get into the brain. Levey 325:7-12. As Dr. Levey conceded, a person of ordinary skill would not view it as reasonable to propose neostigmine as a treatment for Alzheimer's. Levey 325:7-16. To the contrary, Bhasker's lumping together of galantamine with neostigmine would instead confirm to a reader that the article is referring to the use of those cholinesterase inhibitors in arrested dementias like local brain damage, where neostigmine may find use, and not in AD, where it cannot.[8]

Finally, that Bhasker does not describe galantamine as a treatment for AD is confirmed by the way it is described in Excerpta Medica, an abstract service that Defendants rely upon to assert that the Bhasker article was publicly accessible. Def. Br. 20. The Excerpta Medica abstract of Bhasker does not mention Alzheimer's disease, let alone the use of galantamine to treat that disease (or any other progressive dementia). DX 74 at 0002; Coyle 998:20-999:5. To the contrary, Excerpta Medica abstracts Bhasker precisely the way it should be read: "With regard to progressive dementia, there appears to be very little to offer. Only management and no treatment is possible." *Id.*

To maintain their anticipation defense, Defendants must show, by clear and convincing evidence, that Bhasker discloses all the elements of the invention. *See Schumer v. Lab.*

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[8] As Dr. Levey noted, neostigmine may enter the brain in cases of local injury, where the blood brain barrier is damaged. Levey 322:17-22.

Computer Sys., Inc., 308 F.3d 1304, 1315 (Fed. Cir. 2002); *Forest Labs., Inc. v. Ivax Pharms, Inc.*, 438 F. Supp. 2d 479, 486 (D. Del. 2006) (challenger must establish "by clear and convincing evidence that the [prior art] reference contains each and every limitation of the claimed invention"). Moreover, the Federal Circuit has made clear that where, as here, a defendant goes beyond the express terms of a reference and attempts to rely upon how a person of skill in the art purportedly would understand the reference, the defendant bears the burden of showing, by clear and convincing evidence, that the reference necessarily would be understood that way. *See Finnigan Corp. v. ITC*, 180 F.3d 1354, 1365-66 (Fed. Cir. 1999); *see also Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473 (Fed. Cir. 1997) ("An expert's conclusory testimony, unsupported by the documentary evidence, cannot supplant the requirement of anticipatory disclosure in the prior art reference itself.").

In *Finnigan*, the Federal Circuit reversed an ITC finding of anticipation where the reference was silent as to the claim element of "nonresonance ejection" and the ALJ had relied upon the "understanding of one skilled in the art" to fill the gap. 180 F.3d at 1365. The Federal Circuit found that the evidence concerning the understanding of one of ordinary skill was insufficient to support anticipation: "The mere possibility that [the reference] might be understood by one of skill in the art to disclose nonresonance ejection is insufficient to show that it is inherently disclosed therein…As such, *because one skilled in the art would not necessarily recognize that nonresonance ejection is disclosed in the Jefferts article, the evidence is not clear and convincing that the Jefferts article inherently anticipates.*" *Id.* at 1366 (emphasis added); *see also LP Matthews, LLC v. Bath & Body Works, Inc.*, 458 F.Supp.2d 198, 204-05 (D. Del. Oct. 19, 2006) ("an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities").

Here, the Bhasker article does not even approach the level of disclosure required to anticipate an issued patent. Far from necessarily putting a person of ordinary skill in possession of galantamine as a treatment for AD, that article leads such a person away from that conclusion, both by its express description of progressive dementias as untreatable and by its equating of galantamine with neostigmine – thereby reinforcing the understanding of galantamine as a predominantly peripheral agent.

The absurdity of Defendants' reading of Bhasker is demonstrated by the fact that the article was published in 1974, well before the discovery of the cholinergic deficit underpinning any effort to connect cholinesterase inhibitors to AD. Levey 118:21-119:13. Defendants' experts themselves conceded that "to connect galanthamine to Alzheimer's disease with regard to Bhasker, you're going to have to know the whole cholinergic story as it relates to senile dementia of the Alzheimer's type." Domino 486:17-22; *see also* Levey 321:8-322:4. This concession is alone fatal to Defendants' assertion of anticipation. While the doctrine of inherent anticipation allows for testimony concerning the implicit disclosures of a prior art reference, it "does not grant a license to read into the prior art reference teachings that are not there." *See Motorola*, 121 F.3d at 1473; *see also Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576-77 (Fed. Cir. 1991) ("The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill gaps in the reference"); *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991).

III. THE USE OF GALANTAMINE TO TREAT AD WAS NOT OBVIOUS IN 1986

Defendants contend that "[b]oth elements of the claimed invention were well known in the art: that cognitive problems in AD patients could be treated with cholinesterase inhibitors ('CIs') and that galanthamine was a CI that had superior properties for administration to humans." Def. Br. 2-3. The testimony and documents in evidence at trial establish that each of these

propositions asserted by Defendants is wrong. First, in 1986 it was far from obvious that any cholinergic agent – let alone a cholinesterase inhibitor – would succeed as a treatment for AD, and a person of ordinary skill was confronted with a multiplicity of potential approaches, the prospects of success for any one of which were entirely unpredictable. And second, the properties of galantamine known at the time would have led away from its use as a treatment for AD, even to a skilled artisan pursuing a cholinesterase approach.

A. The Law Of Obviousness

Obviousness can only be established by clear and convincing evidence. *Kao Corp. et al. v. Unilever United States, Inc. et al*, 441 F.3d 963, 968 (Fed. Cir. 2006), *reh'g and reh'g en banc denied*. At the heart of any obviousness inquiry are the four *Graham* factors — (a) determining the scope and contents of the prior art; b) ascertaining the differences between the prior art and the claims in issue; c) resolving the level of ordinary skill in the pertinent art; and d) evaluating evidence of objective indicia of non-obviousness. *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). In addition, to find obviousness, a court must also find a reasonable expectation of success in arriving at the invention by combining prior art. *Eli Lilly and Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006).

On the eve of trial in this case, the Supreme Court issued its opinion in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). Contrary to Defendants' assertions, while *KSR* may have done away with a rigid application of the "teaching, suggestion, motivation" (TSM) test, it did not do away with it as a factor to consider. Indeed, the *KSR* Court noted that the TSM test provides a "helpful insight" in any obviousness analysis that must be applied to a generally "expansive and flexible" approach to the obviousness analysis. *KSR*, 127 S.Ct. at 1731, 1739. Most recently, the Federal Circuit and the PTO both interpreted *KSR* to require some explicit rationale for a skilled artisan to combine the prior art in the manner claimed. *See Takeda Chem.*

Indus., Ltd. et al. v. Alphapharm PTY, Ltd. et al., --- F.3d ---, 2007 WL 1839698, at *7 (Fed. Cir. June 28, 2007); United States Patent and Trademark Office Memorandum, "Supreme Court decision on *KSR Int'l Co., v. Teleflex, Inc.*", May 3, 2007. The *KSR* opinion itself states:

> When there is a design need or market pressure to solve a problem and there are a ***finite*** number of ***identified, predictable solutions***, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to ***the anticipated success***, it is likely the product not of innovation but of ordinary skill and common sense.

KSR, 127 S.Ct. at 1742 (emphasis added). Thus, by its own terms, *KSR* did not take aim at patents like the '318 patent — where there were innumerable avenues of exploration and there were no "identified, predictable solutions" to AD at the time of the patent's filing in 1986.

Furthermore, *KSR*'s reference to "predictable" solutions bolsters rather than eviscerates the "reasonable expectation of success" requirement. For there to be a "reasonable expectation of success":

> [O]ne must be motivated to do more than merely to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." Similarly, prior art fails to provide the requisite "reasonable expectation" of success where it teaches merely to pursue a "general approach that seemed to be a promising field of experimentation."

Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006) (internal citations omitted).

Finally, *KSR* left untouched the importance of objective indicia of non-obviousness, which the Federal Circuit stated were "**often be the most probative and cogent evidence [of non-obviousness] in the record.**" *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983) (emphasis added). Integral to any obviousness analysis is a consideration of all

relevant objective indicia of non-obviousness. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80 (Fed. Cir. 1986); *Stratoflex*, 713 F.2d at 1538-39.

B. In 1986, A Person Of Ordinary Skill Was Confronted With A Multiplicity Of Uncertain Options And There Was Considerable Skepticism Of Cholinesterase Inhibitors

Defendants concede that at least three different strategies were pursued to address the cholinergic deficit in AD: precursors (the pre-synaptic approach), cholinesterase inhibitors (the intra-synaptic approach), and direct acting muscarinic receptor agonists (the post-synaptic approach).[9] Def. Br. 7. While Defendants suggest that a cholinesterase inhibitor approach was preferred, the record shows otherwise. In his highly influential 1982 *Science* review, for example, Dr. Bartus identified the post-synaptic approach, using direct-acting muscarinic agonists, as the approach with the "more robust and less variable" results. PX 653 at 413-14; Levey 269:15-24.[10] Dr. Celeste Johns, in a 1983 paper she published with Drs. Ken Davis and Richard Mohs reviewing their work with the cholinesterase inhibitor physostigmine, noted a cholinesterase inhibitor approach was necessarily limited by a dependence upon release of acetylcholine by the pre-synaptic neuron – the part of the cholinergic system particularly degraded by the disease – and she states that "[t]hese problems may be circumvented by administering cholinergic agents which work directly at post-synaptic receptor cites, since the number of post-synaptic muscarinic binding sites is not reduced in SDAT patients as compared

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[9] Professor Wurtman of MIT, in his 1985 publication, identifies seven different strategies for addressing the cholinergic deficit in AD. PX 719 at 276, 277, 279-80. And, as Dr. Domino testified, the situation was even more complicated, since researchers also endeavored to develop compounds that acted in several different ways at once. Domino 491:25-492:11.

[10] Defendants misleadingly quote Bartus for the proposition that physostigmine studies before 1986 "provide the optimist with a basis for hope for future drug development." Def. Br. at 12. What they fail to quote, however, is the last part of that sentence that states "but they admittedly offer no immediate promises of providing effective therapeutic intervention." PX 632 at 343.

to age matched controls." PX 727 at 192. The article goes on to cite promising clinical results from the muscarinic agonist arecoline and to recommend the long-acting muscarinic agonist oxotremorine as potentially a "more ideal compound." *Id.* Thus, the Johns article too – an article Defendants erroneously cite as supporting a cholinesterase inhibitor approach (Def. Br. 11) – in fact recommends muscarinic agonists as a way to overcome the perceived limitations of a cholinesterase inhibitor approach. Levey 279:25-280:23.

Dr. Levey, in a 1995 review, similarly observed that cholinesterase inhibitors were recognized by 1985 to suffer from a lack of specificity between receptor subtypes that suggested they "may not be beneficial" in treating AD. PX 1223 at 870; Levey 305:6-23, 306:10-12. As a result, he noted, the pharmaceutical industry in 1985 began to focus on direct muscarinic agonists. PX 1223 at 870; Levey 306:18-307:2.

Defendants' assertion that cholinesterase inhibitors were the obvious approach in 1986 is also flatly contradicted by the conduct of their own experts. Dr. Levey conceded at trial that, at that time, he viewed muscarinic agonists as the most promising approach. Levey 300:5-7. That is the approach he took in attempting to develop a treatment. Levey 256:20-257:17. Dr. Domino, on the other hand, tried a pre-synaptic approach, using the acetylcholine precursor lecithin along with the metabolic enhancer Hydergine. Domino 468:5-470:15. Hence, neither of Defendants' experts found it obvious in 1986 to pursue a cholinesterase inhibitor approach in their attempts to address the cholinergic deficit of AD.

Far from singling out cholinesterase inhibitors as the "obvious" choice, the cholinergic deficit hypothesis instead led many astray. As Dr. Levey conceded, "logic led in a lot of different directions" and "the consensus was many ways should be approached. **That was all the consensus was about, it's reasonable to try everything that has some scientific rationale.**"

Levey 300:2-4, 17-20 (emphasis added). Admitting that logic pointed in "a lot of different directions" – as Dr. Levey does – is to concede that it does not single out any one approach as obvious. To the contrary, when it is recalled that "logic" led Dr. Levey (and many others) to muscarinic agonists and led Dr. Domino (and many others) to acetylcholine precursors and metabolic enhancers **and that all of those alternative strategies failed**, the only rational conclusion is that what ultimately proved the correct approach, cholinesterase inhibitors, was decidedly not obvious -- let alone the specific cholinesterase inhibitor galantamine, out of the many cholinesterase inhibitors that ultimately failed. *See Takeda Chemical*, 2007 WL 1839698, at *7 (Rejecting obviousness because "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as lead compound for further investigation.")

Two other factors made attempts to develop a treatment of AD in 1986 even more bewildering to a person of ordinary skill. First, the cholinergic deficit hypothesis was only one of many competing theories regarding the right way to develop a treatment for the disease. Thus, in 1986, an AD researcher would have had to consider, in addition to the cholinergic agents, drugs designed to improve blood flow to the brain, those thought to enhance brain metabolism, others intended to correct imbalances in other neurotransmitter systems or neuropeptides, and still others thought to exert a neuroprotective effect. Raskind 1120:9-1122:10; PX 631; PX 714. Each of these approaches were supported by neurochemical evidence, had their champions among the leaders in the AD field, and attracted the attention of the pharmaceutical industry, which conducted clinical trials on each of them. *Id.* Yet all of these approaches failed. PX 1401; PX 1401a. Clearly, AD researchers would not have devoted so many resources – and enrolled so many patients – in these other approaches if cholinesterase inhibitors had been the

obvious strategy for treating the disease.

Metabolic enhancers are a representative example. Prior to 1986, numerous researchers pursued a metabolic enhancer strategy, including recruiting patients into clinical trials of such drugs. Professor Hollister of Stanford described the metabolic enhancers ergoloid mesylates (also known as Hydergine) and piracetam as among the most promising treatment candidates in a 1985 review. PX 631 at 304. Defendants' own pharmacology expert, Dr. Domino, conducted a clinical trial using Hydergine. DX 557; Domino 468:24-470:15.[11] Dr. Raskind participated in clinical trials of oxiracetam, a piracetam analog (a so-called "no-otropic agent"), Raskind 1106:20-1107:13. The goal of these drugs was the same as that of cholinesterase inhibitors – to develop a treatment to alleviate the core symptom of cognitive decline. *Id.*; *see also* Raskind 1102: 15-21. Drs. Domino and Raskind, in enrolling patients in trials of metabolic enhancers, plainly did so with some expectation that they might succeed. Domino 470:9-15; Raskind 1106:20-1108:4. Clearly, they would not have conducted these trials if it were obvious to them that cholinesterase inhibitors were superior.

Second, as of 1986, cholinesterase inhibitors did not stand out as particularly promising. To the contrary, a person of ordinary skill had considerable reasons to doubt the prospects for such an approach. As discussed above, the dependence of cholinesterase inhibitors on the release of acetylcholine by pre-synaptic neurons (discussed in the Johns article) and the lack of specificity between receptor subtypes (referred to in Levey's paper) both cast doubt on the potential of cholinesterase inhibitors to meaningfully enhance cholinergic function in AD

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[11] Indeed, Dr. Domino's published report is encouraging with regard to Hydergine, and he never suggests either cholinesterase inhibitors generally or galantamine specifically as a possible alternative, let alone an obviously superior one. Domino 471:20-472:4.

patients and led many, including Defendants' expert Dr. Levey, away from cholinesterase inhibitors towards a muscarinic agonist approach. See *supra* at page 26.

Equally serious, however, were concerns about the safety and tolerability of cholinesterase inhibitors. Because the cholinergic system operates in both the body and the brain, while AD is, of course, a disease of the brain, a cholinergic agent for AD needed to act predominantly in the brain. Peripheral cholinergic effects are undesirable. Levey 261:20-25; Raskind 1142:13-22. It was recognized at the time that one of the challenges with developing a treatment for AD was overcoming difficulties with safety and tolerability. Domino 465:4-14. Side effects were a particularly important issue in the AD context, where the drug would have to be used chronically, rather than just in an acute fashion. Domino 460:9-461:4.

This problem with side effects was thought to present a particular challenge to cholinesterase inhibitors, which were not thought to be specific to the central cholinergic system. As Professor Wurtman of MIT cautioned in reviewing a cholinesterase inhibitor strategy in 1985, "the problem is one of specificity: A drug that inhibited acetylcholinesterase everywhere, as physostigmine apparently does, would have too many side-effects to be used clinically." PX 719 at 276. While Wurtman noted the theoretical possibility of developing a cholinesterase inhibitor selective for the central cholinergic system, he cautioned that "[a]t present, no such drugs are known." *Id.* at 277. The concern with side effects expressed by Wurtman was widely shared in the AD field (Coyle 881:7-25) causing many researchers to favor highly selective muscarinic agonists over cholinesterase inhibitors. Coyle 885:8-13.

These concerns with both the efficacy and the safety and tolerability of cholinesterase inhibitors made it highly doubtful – and far from obvious – that any cholinesterase inhibitor would be a treatment for AD. In their 1986 review of the AD field, for example, the

distinguished Dutch researchers Drs. Swaab and Fliers outlined a series of neurochemical reasons that, in their view, called for skepticism of "neurotransmitter replacement therapy" – a category that included cholinergic agents such as cholinesterase inhibitors. PX 714 at 421; Raskind 1128:3-16. Their conclusion was that "satisfactory treatment of the cognitive impairment of Alzheimer's disease by means of pharmacologic substitution for deficits in the cholinergic system seems at present not to be feasible." PX 714 at 421, 419.

To be sure, doubts about a cholinesterase inhibitor approach did not entirely stop work on cholinesterase inhibitors. But this skepticism does make clear that cholinesterase inhibitors were far from the obvious choice. To the contrary, a person of ordinary skill would have been confronted with a bewildering array of options, each supported by its own logic and evidence; and he or she could not have predicted which approach, if any, might be the right one. Raskind 1120:9-24. This is the antithesis of obviousness. *See Medichem*, 437 F.3d at 1165.

C. Galantamine's Known Pharmacologic Properties Would Have Led Away From Its Use As A Treatment For AD

Defendants make the remarkable assertion that "Galanthamine fit the criteria for the next generation of reversible tertiary amine CIs perfectly." Def. Br. 12. Nothing could be further from the truth. To the contrary, the trial record establishes that with regard to the relevant pharmacologic properties – galantamine's peripheral activity, its potency, its cholinergic selectivity, and its duration of action – what was known about galantamine led away from its use as a treatment for AD. Indeed, as discussed above, it was only through new insights about both galantamine's therapeutic activity and the cholinergic deficit of AD that Dr. Davis was able to arrive at her invention. See *supra* at pages 8-11.

1. Peripheral Activity. As of 1986, galantamine was primarily used for peripheral nervous system diseases. In Europe, galantamine (known as Nivalin) treated disorders of the

neuromuscular junction or was used to terminate the polarizing effect of anesthetic agents at the neuromuscular junction or as an antidote for curare – peripheral, nicotinic disorders. Coyle 883:1-6. For example, the Pernov article (PX 1181), which Defendants cite as instructive of galantamine's properties known in 1986 (Def. Br. 24), instructs that galantamine's "therapeutic range of application above all encompasses disease of the neuromuscular apparatus – myasthenia gravis, pseudoparalytica, dystrophia musculorum progressiva, and disease of the peripheral motoric neuron." PX 1181 at 05984. Defendants' expert conceded that Pernov teaches that galantamine "has a lot of activity in the periphery" and that "[i]n terms of a person in 1986 reading this, they would see it as being above all peripheral and nicotinic." Levey 263:17-264:5. More generally, he acknowledged that galantamine's "use in the literature had been for peripheral nicotinic effect, myastenia gravis." Levey 276:1-5. [12]

A cholinesterase inhibitor with predominantly peripheral effects is precisely the opposite of what one of skill in the art would have been looking for in 1986. As Dr. Levey conceded, because AD is characterized by a deficiency in the central cholinergic system, a desirable cholinesterase inhibitor would have activity predominantly in the brain, and "[p]eripheral cholinergic effects were undesirable." Levey 261:20-25. *A fortiorari*, a cholinesterase inhibitor like galantamine that was seen as "above all peripheral" and as having "a lot of activity in the periphery" would appear undesirable to a person of ordinary skill seeking a cholinesterase inhibitor to treat AD. Coyle 915:7-10 ("Well, obviously, Alzheimer's disease is a disease of central cholinergic neurons and [galantamine] as a drug that works – is perceived to work

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[12] Defendants suggest that galantamine was used for central nervous system disorders. Def. Br. at 14. However, this is contradicted by Defendants' own expert testimony, that galantamine was known, "above all" as a peripheral, nicotinic agent (Levey 263:2-16) — many of the disorders Defendants now point to, like cerebral palsy, are motoric rather than cognitive, and are thus unlike AD. Raskind 1143:9-1145:11.

primarily in the periphery would not – not be an attractive candidate.").[13]

Indeed, to a person of ordinary skill, galantamine's peripheral action would have weighed especially heavily against its use in AD, a chronic condition where peripheral cholinergic side effects were a particular concern. See *supra* at pages 29-30. The widely perceived failure of the leading cholinesterase inhibitor, physostigmine (Domino 462:10-18), would have exacerbated this concern, since, among other things, physostigmine was seen to have too many peripheral cholinergic effects to be used in treating AD. Levey 173:12-23; Domino 463:4-11. Defendants themselves take the position that physostigmine's failure would have motivated researchers to find agents that "had less peripheral side-effects than physostigmine." Def. Br. 12.[14] This would point directly away from galantamine, whose principal use was peripheral. As Dr. Raskind explained regarding galantamine's prior use as a peripheral cholinergic agent:

> It would diminish interest because in terms of strategies to enhance any neurotransmitter system and certainly the cholinergic system and certainly for cholinesterase inhibitors, we were trying to find compounds that had substantially more activity in the brain, where we wanted to get therapeutic on memory and other cognitive functions, with low or hopefully minimal effect on the periphery, because the periphery is where we experienced these side effects that made the drugs so difficult to use. (Raskind 1142:13-22)

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[13] Dr. Levey admitted at trial that the cholinesterase inhibitor neostigmine would not have been seen as a reasonable candidate to treat AD specifically because it has "better peripheral action." Levey 325:7-16. This implicitly concedes that cholinesterase inhibitors thought to have predominantly peripheral effects would not have appeared to be reasonable candidates to treat AD. In this regard, too, Bhasker's reference to galantamine and neostigmine together would reinforce galantamine's peripheral activity and lead away from its use for AD.

[14] Remarkably, Defendants nonetheless put great weight on the physostigmine literature. But all of the experts and the parties agree that physostigmine had failed as a treatment for AD by 1986. Moreover, as shown, that failure led away from galantamine – a less potent, no longer acting cholinesterase inhibitor whose therapeutic effects were principally peripheral and nicotinic. Additionally, Defendants grossly misstate the physostigmine literature, which, as discussed in the text, did not indicate that a cholinesterase inhibitor would succeed as treatment for AD. Indeed, Defendants even overstate the amount of that literature. While there may have been 14 publications, all of those publications were based on a small number of studies.

Defendants point to the fact that "galantamine reversed scopolamine-induced amnesia, which was an early model of AD" in support of the proposition that galantamine was known to "penetrate the brain" and inhibit cholinesterase there. Def. Br. 13. But this misses the mark. The fact that galantamine could penetrate the brain does not change the fact that its predominant activity was believed to be in the periphery. Because scopolamine-induced amnesia is an acute condition (Domino 462:2-6; Coyle 886:21-887:5), the ability to reverse scopolamine-induced amnesia would not indicate that a cholinergic agent had the necessary predominance of central over peripheral effects to be a treatment for AD.

This point would have been particularly evident to a person of ordinary skill in the art at the time, given the failure of physostigmine as a treatment for AD. As Dr. Domino acknowledged, unlike galantamine, physostigmine was actually approved by FDA for the treatment of scopolamine-induced delirium, under the trade name Antilirium, and hence was known to be safe and effective for that use, even though it proved not to be for AD. Domino 461:14-462:18. Thus, galantamine's ability to reverse scopolamine-induced delirium would in no way indicate that galantamine had fewer peripheral effects than physostigmine – to the contrary, galantamine's established therapeutic use for peripheral cholinergic disorders, in contrast to physostigmine's approved use as Antilirium, would have made galantamine appear even more peripheral than physostigmine.[15]

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[15] Defendants fail to note that the scopolamine model served not to establish the effectiveness of drugs against AD but rather to find the "pharmacologic targets" of drug therapy, specifically, to establish the significance of the central muscarinic receptor. Coyle 871:9-18. In addition, scopolamine was used as a model for the cholinergic deficit in AD. It was also recognized to be a very limited one. Coyle 848:13-20. As Dr. Davis explained in distinguishing prior art showing galantamine's effect on scopolamine-induced amnesia: "It teaches that galantamine reverses the amnesia-producing effects of scopolamine. However, this would be expected of an anticholinesterase. Nothing in this teaching leads to an expectation of utility against AD. There (continued...)

2. Potency. Galantamine was known as a weak cholinesterase inhibitor, "much weaker than physostigmine and much weaker than tacrine." Coyle 909:10-12. Inexplicably, Defendants assert that the trial record shows "without contradiction" that galantamine's potency was better than physostigmine. Def. Br. 14. Yet, Defendants' own expert pharmacologist, testified that galantamine was "absolutely" known to be a weak cholinesterase inhibitor: "from the data in the literature that I have reviewed, it's on the order of about a tenth of the potency of – of physostigmine." Domino 416:3-9. Dr. Levey agreed. Levey 340:14-16. So, directly contrary to Defendants' position, the "uncontradicted" trial record is that galantamine's potency was, at best, thought to be an order of magnitude smaller than physostigmine.

As noted previously, galantamine's lack of potency would have been discouraging to a person of ordinary skill because "that means you have to use more of it … and the more of it you have to use, the greater the likelihood that the drug is going to interact with other processes and cause side effects." Coyle 909:2-7. As Dr. Domino acknowledges, galantamine's lower potency means that cholinesterase inhibition could only be achieved by increasing the dose. Domino 416:18-20 ("Multiply it by ten."). Yet he also acknowledges that a known way of attempting to address peripheral cholinergic side effects is to lower the dose. Domino 436:3-8; 461:5-11. Needless to say, it is impossible to simultaneously increase the dose to address low potency and decrease the dose to address side effects. Coyle 1006:12-23.

Similarly, Dr. Levey, in a 1996 publication, wrote that "[p]resently used, cholinergic compounds [a category including cholinesterase inhibitors, Levey 339:6-340:3] suffer from a lack of subtype selectivity and potency, which favor negative peripheral side effects and may

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are many anticholinesterase drugs available but AD is still regarded as being effectively untreatable." PX 14 at 6.

limit cognitive effects because of weak and/or opposing actions in the brain." PX 1228 at 13545. He too agreed that galantamine's lower potency would make it seem less promising as a treatment for AD. Levey 335:4-20.

3. **Cholinergic selectivity.** As noted, the prior art described galantamine's therapeutic action as, above all, peripheral and nicotinic. Levey 264:3-5; 276:1-5. The other side of galantamine's predominantly nicotinic effect is of course its weak muscarinic effect. Thus, the Cozanitis 1971 article – "an important article" (Domino 486:2-6) – specifically points out, as a factor "that must be borne in mind," the fact that galantamine has "very slight muscarinic effect." PX 1339 at 420; Levey 312:25-313:11. The 1965 Stojanov article similarly describes galantamine's use as a nicotinic agent, with weak muscarinic effects. PX 1350 at 685 ("Its muscarinic effect is slight."); Levey 316:19-23.

As discussed above, at the time, the cholinergic deficit hypothesis of AD was focused on the central muscarinic system, based on the association between the muscarinic system and memory and the failure of nicotinic blockers (unlike muscarinic ones) to mimic geriatric memory loss. See *supra* at pages 6-7. The experts agree that a cholinergic agent having weak muscarinic effects would not, in 1986, have been considered to have potential as a treatment for AD. Dr. Levey's testimony in this regard is unequivocal. Levey 273:4-21, 276:16-20. [16]

4. **Duration Of Action.** Defendants acknowledge that, in 1986, those pursuing a cholinergic approach were looking for cholinergic agents "that were longer acting than physostigmine." Def. Br. 27. Although Defendants contend that galantamine was known to be

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[16] Dr. Coyle similarly testified that, on the basis of the work done comparing the effects of muscarinic and nicotinic blockers, a person of ordinary skill would be discouraged from pursuing "a drug that was known to be a weak muscarinic agent but to have nicotinic effects." Coyle 870:20-872:13.

longer-acting than physostigmine, the testimony to that effect was based on a study published by Westra after 1986 showing a half-life for galantamine of roughly 4 hours. Domino 481:18-482:3. Prior to Westra's work, the available evidence suggested a duration of action for galantamine of about 2 hours – the same as that observed for physostigmine. Levey 334:15-23; Raskind 1147:18-1148:2. And in either case, galantamine would not be viewed as having a significantly greater duration than physostigmine, as evidenced by Domino's 1988 review describing galantamine, even after the publication of the Westra work, as "not a very long acting compound" and as "less potent than physostigmine and with a similar duration of action." PX 756 at 301.[17] In either case, galantamine was not so long-acting as to be obviously superior to physostigmine, and a person of ordinary skill, looking for a long-acting cholinergic action, would not have viewed galantamine as a promising candidate. Raskind 1211:14-23.

In sum, the properties of galantamine known as of 1986 — a weak and short-acting cholinesterase inhibitor with predominantly peripheral, nicotinic effects — was the opposite of what the AD field was looking for and would not have been considered a candidate for treatment for AD by a person of ordinary skill. Defendants attempt to blur this clear record by two misleading arguments. First, Defendants erroneously cite to several documents prepared by Dr. Davis describing the logic behind using galantamine for AD as purported evidence that such use of galantamine was obvious. Def. Br. 26-27 (quoting DX 651 and PX 595). However, it is settled law that an obviousness defense cannot be based upon the inventor's own view of the

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[17] To be sure, there is literature, such as Baraka, that describes galantamine as longer acting than physostigmine. However, as Dr. Raskind testified, a review of the data set forth in the papers contradicts that assertion. Raskind 1146:5-1147:10. Indeed, Dr. Domino, in his 1988 review, similarly concluded that Baraka did not demonstrate a longer duration of action for galantamine and, as noted, he too concluded that galantamine's duration was similar to physostigmine's. PX 756 at 297; Levey 334:15-23.

logic of her invention. See *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985); see also *In re Lee*, 277 F.3d 1338, 1344 (Fed. Cir. 2002) ("It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to '[use] that which the inventor taught against its teacher.'") (quoting *W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983)) (alteration in original). Moreover, Defendants fail to disclose that the cited documents were prepared after the issuance of Dr. Davis' patent, at a time when she was trying to convince a pharmaceutical company to develop a galantamine drug. Viewed in that context, the more telling evidence is the response of the pharmaceutical companies to the "obvious" case she made to them – namely, skepticism and rejection. See *supra* at pages 14-16. Hence, far from demonstrating obviousness, Dr. Davis' efforts to garner interest in a galantamine product instead further confirm the non-obviousness of her invention, which was contrary to the conventional wisdom of the time.

Second, Defendants cite to a 1997 publication by Dr. Michael Rainer and Dr. Domino's 1988 review as evidence of simultaneous invention. But Dr. Rainer's unsubstantiated assertion – more than 10 years after Dr. Davis' patent application and in the midst of a patent dispute with Dr. Davis in Austria – does not suffice to establish simultaneous invention. *See, e .g., Finnigan*, 180 F.3d at 1368 (rejecting uncorroborated allegations of anticipating prior sale: "It is not surprising that the cases have held that testimony concerning a witness's **own** anticipatory activities must be corroborated. A witness who testifies to antedating the invention of the patent-in-suit can be expected to derive a sense of professional or personnel accomplishment in being the first in the field, and in this sense is not uninterested in the outcome of the litigation, even if that witness is not claiming entitlement to a patent").

Of course, the same holds true for Defendants' assertion, based on Dr. Domino's 1988

review article, that Dr. Domino also simultaneously conceived of galantamine for Alzheimer's. But Dr. Domino acknowledged at trial that the article had first been proposed in the Fall of 1987, in a discussion with Dr. Giacobini. Domino 413:6-19. Dr. Giacobini, a well-regarded expert in cholinesterase inhibitors, would certainly have been aware of Dr. Davis' patent and Dr. Coyle's subsequent animal studies on galantamine in an animal model of AD. Raskind 1275:8-1276:7.

Dr. Domino's true, contemporaneous view of galantamine is evidenced by the work he actually published before 1986 – a report of a clinical trial of Hydergine for AD. Despite being knowledgeable of galantamine from his time in the Soviet Union in the early 1970s, Dr. Domino neither used nor proposed galantamine for AD at that time. Domino 471:24-472:4. Surely, had galantamine truly been obvious to Dr. Domino as a treatment for AD at the time, he would have written about it prior to 1986.

The first Dr. Domino wrote of galantamine for AD was a 1988 abstract of the talk Dr. Giacobini had asked him to give. PX 153. In his abstract, Dr. Domino reports that: "We concluded, on the basis of this preliminary evidence in rats [concerning galantamine's duration of action], **that galanthamine has no advantage over physostigmine**." *Id.* (emphasis added). This is a particularly damning statement when it is recalled that, to Dr. Domino at the time, physostigmine was a "waste of time." Domino 464:7-12. Surely, if Dr. Domino had already recognized galantamine as a treatment for AD, he would not have stated, to the contrary, it had "no advantage" over another compound he had already concluded was a "waste of time."

D. That Galantamine Was Not An Obvious Treatment For AD Is Confirmed By Objective Considerations

Objective indicia of non-obviousness also demonstrate that galantamine was not an obvious treatment for AD.

Long-Felt But Unmet Need. There can be no serious dispute that, by 1986, there was a

long-felt but unmet need for a treatment of AD. As discussed above, by 1986, AD was recognized as epidemic among the elderly, imposing a terrible toll of cost and suffering on society as a whole. See *supra* at pages 4-5; *see also* PX 663 at 1184 (Coyle 1983: "One of the most feared and devastating aspects of aging is the deterioration of memory and other mental processes that occurs with increasing frequency in advancing years."). Yet, by 1986, there were no therapies or treatments available for AD sufferers. Raskind 1080:16-21. As Dr. Leber of FDA stated during a 1989 Agency Symposium, "[a]t this point in time, even a safe and effective symptomatic treatment for some cardinal sign and symptom of Alzheimer's would constitute a substantive therapeutic advance." PX 1122 at 10. This statement was equally true three years before, in 1986. Levey 284:9-285:20.

Failure Of Others. As Defendants' expert Dr. Levey acknowledged, AD has proved a "tough disease" and a "tricky disease." PX 1401; PX 1401a. As noted above, in addition to cholinergic approaches, AD researchers have conducted clinical trials on drugs to improve cerebral blood flow, to enhance brain metabolism, to correct imbalances in other neurotransmitter systems or neuropeptides, and still others thought to provide neuroprotection. Raskind 1120:9-1122:10; PX 631; PX 714. Even the narrower field of cholinergic strategies is littered with failures. As discussed above, in addition to cholinesterase inhibitors, researchers conducted clinical trials of acetylcholine precursors and direct muscarinic agonists. These too all failed. The field of cholinesterase inhibitors has shown similar futility. At least 38 different cholinesterase inhibitors have been tried as therapies for AD. Levey 289:11-25; PX 214. Only four have shown an efficacy in treating AD, and one (tacrine) is not prescribed because of safety problems and another (rivastigmine or Exelon) has tolerability problems that limits its use. Levey 286:3-287:23; PX 1401a. The vast majority of cholinesterase inhibitors have failed.

Unexpected Benefits. In the two decades since 1986, evidence has accumulated that not only is galantamine a safe, effective, and tolerable treatment for AD, it works in unexpected ways and yields unexpected results. First, an unexpected explanation has emerged for how, despite its weak potency as a cholinesterase inhibitor, galantamine is nonetheless able to provide therapy for AD. Specifically, it has been discovered that galantamine enhances cholinergic function in two ways – not only inhibiting cholinesterase but also positively modulating the nicotinic receptor, making it more response to stimulation by acetylcholine. Coyle 852:4-11; 916:6-23. This nicotinic "allosteric modulation" enhances galantamine's nicotinic effects relative to its muscarinic ones (Coyle 916:3-14) and has been recognized in the scientific literature as the "prime candidate" to explain how galantamine succeeds despite its low potency as a cholinesterase inhibitor. PX 680 at 192; Coyle 921:12-924:15.

Evidence also shows that galantamine does more than treat the symptoms of AD; it actually slows disease progression. Dr. Domino conceded that, beginning in the 1990s, Dr. Giacobini, a leading expert on cholinesterase inhibitors, proposed neurochemical mechanisms by which cholinesterase inhibitors might impede the underlying disease process. Domino 494:11-496:8; Coyle 929:21-930:22. Long term studies with galantamine have since shown evidence of this. First, patients who delay starting on galantamine do not "catch-up" to those who started earlier – an indication that the earlier therapy not only provided symptomatic improvement, but also slowed its progression. Raskind 1164:8-19. Second, three-year studies of the drug have shown that AD patients on galantamine for three years decline at a slower rate than historical averages, additional evidence that the drug is going beyond symptomatic relief to alter the disease process. PX 706; Raskind 1167:15-1171:11.

Defendants argue that because FDA has not permitted galantamine's allosteric

modulatory effect and impact on disease progression to be included in Razadyne's labeling, the evidence supporting those benefits should not be considered. But FDA approval has never been a requirement for supporting patentability. *See In re Brana*, 51 F.3d 1560, 1567-68 (Fed. Cir. 1995). Here, the trial record shows that galantamine's effects are well accepted in the scientific community. Raskind 1173:5-1174:1. The absence of labeling reflects not uncertainty in the science, but the inability to conduct long-term, double-blind studies because of ethical concerns arising from the withholding of treatment that would be implicit in a placebo-controlled study. Coyle 931:10-21. The evidence supporting galantamine's unexpected benefits are, in Dr. Raskind's words, "real and as rigorous as one can do, given the ethical constraints of doing long-term controlled placebo study in Alzheimer's disease." Raskind 1172:18-21.

Skepticism. As discussed above, there were considerable doubts expressed about a cholinesterase inhibitor approach, and it was not predictable that such an approach would succeed. See *supra* at pages 7-8 and 14-16.

Licensing And Acquiescence. Dr. Davis succeeded in getting three different licensees for the invention claimed in the '318 patent. PX 1397; PX 1398; PX 305; PX 329; DX 629. In addition, by filing ANDAs but agreeing to stay off the market until the expiration of the patent, 11 different ANDA-filers have also acquiesced to the validity of the '318 patent. PX 810; PX 811; PX 812; PX 818; PX 820; PX 1245; PX 1246; PX 1247; PX 1248; PX 1364; PX 1365 (note that one Paragraph III filer that did not provide a declaration of authenticity).

Commercial Success. Commercial success is ordinarily judged by revenues of a product that embodies a patented invention. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). By that standard, Razadyne, the embodiment of the '318 patent, has been an unqualified commercial success, grossing over **REDACTED** in revenue over the first five

years of sales. PX 1402 **REDACTED** [18].

IV. THE '318 PATENT MEETS ALL THE REQUIREMENTS OF ENABLEMENT

A. A Skilled Artisan Is Enabled To Practice The Invention

A patent is enabled if "one reasonably skilled in the art could make or use the [patent's] invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). A patent is enabled even if those of ordinary skill must undertake some experimentation in order to practice the invention so long as that experimentation is not "unduly extensive." *Hybritech*, 802 F.2d at 1384. For the '318 patent to be invalidated on enablement grounds, Defendants must prove by clear and convincing evidence that those of ordinary skill reading the '318 patent could not, without undue experimentation, use galantamine for the treatment of AD and related dementias. *See Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993). The enablement requirement does not obligate inventors to describe their theory of the invention or how it was conceived. *See Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed. Cir. 1983) ("It is undisputed that inclusion of [the inventor's] theory and belief was unnecessary to meet the enablement requirement of 35 U.S.C. § 112.").

The parties' experts agree that the patent does enable a person of ordinary skill to practice the invention. Dr. Levey's conceded that one of ordinary skill in the art could use the '318 patent to treat AD. Levey 328:17-329:3. Dr. Raskind similarly agreed that "a person of ordinary skill in the art in 1986 reading the patent [would] be enabled to practice the claimed invention by

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[18] Defendants' assertion that royalties paid to the patent-holder count against commercial success again erroneously turns a positive factor – licensing – against commercial success. Indeed, under Defendants' approach, the larger the royalty paid for the patent, the less commercially successful the invention – an absurd result.

administering galanthamine as a treatment for Alzheimer's disease." Raskind 1180:2-6.

The experts also agree that a person of ordinary skill reading the patent would be able to find a therapeutically effective dose of galantamine. As Dr. Raskind explained, this would be achieved through the standard clinical practice of dose titration. Raskind 1178:23-1179:8 (those of ordinary skill "would start at a low dose, as described in the patent, and then they would gradually titrate the dose upward to the point where they either saw therapeutic effects or the patient developed adverse effects, which were troublesome enough to stop any further increase of the medication."). Dr. Levey agreed that one of skill in the art in 1986 would have known the therapeutically effective dose (Levey 222:23-223:2) and would be able to "find therapy in an effective dose," Levey 328:17-329:3. And the patent similarly instructs one skilled in the art to use titration to find the appropriate dose of galantamine in the treatment of AD. PX 1 at col. 1, ll. 64-66; Raskind 1178:18-1180:1. Defendants do not contend that a person of ordinary skill reading the patent would be unable to practice the invention.[19]

At the close of trial, the Court inquired whether, "titration would be very tricky with galantamine [for use as treatment in AD] because there are no immediate effects, just a slowing of an inevitable decline." Trial Tr. 1417:18-21. While it is true that many patients do not see an improvement in cognition, that would not prevent titration to a therapeutically effective dose.

The experts agree that the cognitive decline associated with AD was steady and

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[19] The one exception to this is that Defendants argue that Claim 4 of the patent is not enabled because the dosage range set forth in the claim is too broad. Def. Br. 49. However, the case on which Defendants erroneously rely, *Imperial Chemical Industries v. Danbury Pharmacal, Inc.*, 777 F. Supp. 330 (D. Del. 1991), involved an entirely new chemical entity for which no dosing information was available. Here, by contrast, galantamine is an old compound for which extensive dosing information existed. Levey 230:21. Dr. Davis' invention was the use of galantamine to treat AD; once that novel and non-obvious leap was made, dosing information could be derived from reasonable experimentation in light of known dosing schedules. Domino 407:16-20; Raskind 1178:18-1179:3. Under these circumstances, Claim 4 is also enabled.

predictable. Levey 100:2-19; Raskind 1071:13-1072:20. They also agree that a typical effect of the drug is to maintain the patient's cognitive function, preventing deterioration and stabilizing the patients condition for about a year. Raskind 1167:15-19; Levey 109:7-14; PX 704 at 2265. Because the disease is known to be relentlessly progressive, a person of ordinary skill following the patent would be able to titrate to a therapeutic dose by observing the absence of decline.[20] In this regard, it is worth noting that the patent itself sets forth preferred dosing for a galantamine hydrobromide product that corresponds to the dosage ranges currently approved and used today. *Compare* PX 1 at col. 2, ll. 60-66 *with* DX 655.[21]

B. The Patent Sets Forth Adequate Evidence Of Utility To Be Enabled

While conceding that the patent does enable a person of ordinary skill to practice the invention, Defendants instead assert that the patent is not enabling because it contains insufficient evidence of galantamine's utility in treating AD. Defendants make much of the Federal Circuit's opinion in *Rasmusson v. SmithKline Beecham*, 413 F.3d 1318 (Fed. Cir. 2005). A close examination of *Rasmusson*, however, makes clear that it is inapplicable to this case both on the law and the facts.

First, despite Defendants' arguments to the contrary, *Rasmusson* does not require a showing of ultimate effectiveness in treating a particular indication in order for a patented invention to be enabled. All that is required is that the patent allow those of ordinary skill in the art to practice the invention without undue experimentation. *Hybritech*, 802 F.2d at 1384.

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[20] Further, practitioners were experienced in administering tests to monitor the degree of decline in an AD patient. *See e.g.* Levey 137:18-138:4, 144:17-23, 154:21-155:3; Raskind 1162: 22-25.

[21] To be sure, as Dr. Raskind suggested, titration to the absence of decline in actual practice required the medical community to abandon their skepticism of treatments for AD. Raskind 1173:21-1174:20. But that testimony confirms that physicians are able to titrate to the absence of decline, and the prevailing skepticism is, if anything, evidence of validity.

Unlike this case, *Rasmusson* involved an *inter partes* interference proceeding before the PTO — before a patent had issued and in circumstances where the PTO had determined that the patent application at issue did not contain adequate evidence of utility. As the Federal Circuit said in *Rasmusson*, "it is proper *for the patent examiner* to ask for substantiating evidence *unless* one with ordinary skill in the art would accept the allegations as obviously correct." *Rasmusson*, 413 F.3d at 1323 (quoting *In re Jolles*, 628 F.2d 1322, 1325 (Cust. & Pat. App. 1980)) (emphasis added). Here, the patent examiner did not ask for clinical or preclinical data during the prosecution of the '318 patent. Instead, it was the patentee (Dr. Davis) who offered to provide such data to the examiner (PX 14 at 2) and it was the examiner, convinced by Dr. Davis' application and other submissions that all the requirements of patentability had been met, who issued a notice of allowability without requiring more data. Notice of Allowability (in PX 2). Under these circumstances, Dr. Davis was not obligated to provide additional evidence of utility. *See In re Brana*, 51 F.3d at 1566 ("From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure...**Only after the PTO provides evidence** showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.")(emphasis added).

Second, Defendants' asserted defense fails on the facts. As the trial record makes clear, the patent does set forth adequate evidence of utility (as the patent examiner implicitly found). While short, the patent disclosure describes both the new model for the cholinergic deficit in AD that rendered galantamine's central nicotinic effects relevant and the evidence, mined from the technical literature, that showed that galantamine had the requisite properties to succeed in that model. B. Davis 709:10-711:21, 713:8-715:12; Coyle 889:20-890:20; 980:21-981:1; Raskind

1187:3-1190:20, 1271:25-1273:5.

That the disclosure in the patent was sufficient evidence of utility is confirmed by actual events. When Dr. Davis first approached Dr. Coyle to conduct the animal testing, in 1986, she had no evidence beyond what was set forth in her patent. Yet, confronted with that case, Dr. Coyle concluded that it was "well grounded and – and it fit in very nicely with the lesion model because that was the model where you could really see if there was contribution of nicotinic receptors to – you know, to the effects of acetylcholinesterase inhibitors." Coyle 890:3-9. The proposal "connected the dots": "Galanthamine in humans safe and well tolerated. Cholinesterase inhibitor, selective nicotinic effects, and very modest muscarinic side effects." Coyle 980:21-981:1. Indeed, Defendants' Dr. Levey agreed that Dr. Davis' idea of using galantamine as a treatment for AD in 1986 was scientifically reasonable. Levey 330:23-331:1. The patent speaks clearly to a person of ordinary skill. Raskind 1189:2-1190:20; Coyle 890:3-9.

Defendants argue that the evidence in the patent cannot to establish utility because the record shows that a person of skill in the art would not "accept 'without question' Dr. Davis' claim that galanthamine treats AD." Def. Br. 43. But that is not the correct standard. As Defendants' own quotation from *Rasmusson* makes clear, the case held (in the context of a patent examiner's request for evidence prior to patent issuance) that:

> [w]here there is no indication that one skilled in [the] art **would accept without question** statements [as to the effects of the claimed drug products] and **no evidence** has been presented to demonstrate that the claimed products have those effects, an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement.

Def. Br. 41 (quoting *Rasmusson*, 413 F.3d at 1323 (emendations and emphasis in Defendants' brief)). As the quote makes clear, even were *Rasmusson* to apply here, all it requires is that **either** utility be accepted without question **or** that some evidence of utility be included. There is

no requirement that the evidence establish utility beyond all question – a standard that would ring the death knell of pharmaceutical patents. As Defendants' expert admitted, to prove that a drug would work as a treatment for AD, one would need large phase II or phase III clinical trials. Levey 331:11-332:7. The Federal Circuit has already rejected Defendants' position, warning that "[w]ere we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas." *In re Brana*, 51 F.3d at 1568. The Court expressly held that enablement is satisfied well before a drug is ready for human trials:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.

Id. This is in accord with practice in the AD field, where (in Dr. Levey's own words) it is "[a]bsolutely not" industry practice to "wait to file patent applications until phase two or phase three [clinical] trials are underway." Levey 332:12-15.

Nothing in *Rasmusson* or elsewhere forbids the inventor from relying in part on the existing data in the prior art to establish utility. In fact, the Federal Circuit in *In re Brana* held that the inventor *may* rely on such data. *See* 51 F.3d at 1567 ("The prior art further supports the conclusion that one skilled in the art would be convinced of the applicants' asserted utility."). Here, because the patent provides data – in the form of galantamine's effects as determined in prior experiments – and connects that data to show an expectation of utility through the animal lesion model set forth in the patent, the requirements of section 112 are met. There is no further requirement that the patent establish utility "beyond question."

Defendants also assert that Plaintiffs lack any competent evidence of utility because Dr.

Raskind's testimony was purportedly outside the pre-trial disclosure in his expert reports and deposition. Def. Br. 46-47. As an initial matter, Defendants put the shoe on the wrong foot – it is their burden to prove lack of enablement by clear and convincing evidence, and not Plaintiffs to prove the patent enabled. *See Morton Int'l*, 5 F.3d at 1470. More fundamentally, Defendants accusation is wrong both as to the foundation for Dr. Raskind's testimony and about the available record evidence supporting enablement.

Because the foundation for Dr. Raskind's testimony lies in documents outside the trial record (namely, his three expert reports and deposition), Defendants' accusation will be addressed in a separate paper. However, it can be noted here that the foundation for that testimony is the patent's use of the new animal model for AD combined with galantamine's properties. Even the small excerpt from Dr. Raskind's trial testimony concerning his expert reports that Defendants' quote in their brief makes clear that those reports highlighted Dr. Raskind's opinion that, in enabling Dr. Davis' invention, the "most significant" disclosure in the patent is the animal testing model for confirming effectiveness in AD. Def. Br. 46 (quoting Raskind 1198:9-11, 1199:9-17). And Defendants omit from their excerpt the very next portion of Dr. Raskind's cross-examination concerning his expert disclosure, connecting an expectation of utility with the animal model itself. Raskind 1199:20-1200:8. Dr. Raskind clearly provided the Defendants with adequate notice of his opinion to pursue the question further in deposition.

Defendants also err in asserting that enablement here is supported only by Dr. Raskind's testimony. In fact, both Dr. Davis and Dr. Coyle testified as well about how the combination of Dr. Davis' insights concerning the properties of galantamine combined with the new animal model for AD would provide a scientifically grounded expectation of galantamine's utility in treating AD. Their testimony too suffices to defeat Defendants' enablement defense, without

regard to Dr. Raskind's testimony on this point.

Finally, Defendants attempt to denigrate Dr. Davis' insights by labeling them an "*ex post facto* attempt to save the patent." Def. Br. 47. Even this were true, it would be irrelevant, since an inventor is not required to understand the basis for her invention. *Fromson*, 720 F.2d at 1570. But here it also happens to be untrue. In the prosecution history, Dr. Davis criticizes the scopolamine model of AD as irrelevant to efficacy in treating AD and proposes instead the data from the animal lesion model as establishing efficacy. PX 14 at 6, 2. She made a similar point shortly after the patent issued, when she was attempting to get the drug developed. PX 1061 at 2 ("Given the loss of nicotinic as well as muscarinic agonism resulting from the ACh deficiency in Alzheimer's, and the failure of muscarinic agonists to have significant cognitive effects, I wouldn't take scopolamine dementia to be a model of Alzheimer's disease.").

Defendants' major complaint seems to be that Dr. Davis used the language of results – galantamine's effects on cortisol levels, reversal of impairments on learning and retention – rather than mechanism. But the record is clear that the patent would be understood by a person of ordinary skill in the art. That is sufficient.

CONCLUSION

Based on the evidence offered at trial and the argument above, this Court should find:

1. **Anticipation:** Defendants have failed to show by clear and convincing evidence that Bhasker anticipates the '318 patent because: i) Bhasker does not even mention AD, ii) it asserts that progressive dementias (like AD) cannot be treated, and iii) it mentions galantamine only once and only for the treatment of arrested dementias (like tumor and local brain injury).

2. **Obviousness:** Defendants have failed to establish by clear and convincing evidence that the use of galantamine for AD was obvious as of January 15, 1986 because: i) there

were a multiplicity of uncertain options for treatment of AD in 1986, ii) there was considerable doubt about the prospects of cholinesterase inhibitors, iii) galantamine's known pharmacological properties would have led away from its use as a treatment for AD due to galantamine's peripheral activity, lack of potency, lack of cholinergic selectivity and short duration of action, and iv) multiple objective indicia of non-obviousness — long felt but unmet need, failure of others, unexpected benefits, skepticism, licensing and acquiescence, and commercial success.

3. **Enablement**: Defendants have failed to show by clear and convincing evidence that the '318 patent is not enabled because: i) one of ordinary skill is enabled to practice the invention, and ii) the patent provides adequate evidence of utility.

For the aforementioned reasons, the Court should enter judgment in favor of Plaintiffs that the '318 patent is infringed and not invalid.

CERTIFICATE OF SERVICE

I hereby certify that on the 30th day of August, 2007, the attached **REDACTED PUBLIC VERSION OF PLAINTIFFS' POST-TRIAL ANSWERING BRIEF** was served upon the below-named counsel of record at the address and in the manner indicated:

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